Persistent replicative stress alters polycomb phenotypes and tissue homeostasis in Drosophila melanogaster.

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Public Summary:
Polycomb group (PcG) proteins establish and maintain genetic programs that regulate cell-fate decisions. The Drosophila multi sex combs (mxc) gene was previously categorized as a PcG gene; however, a mechanistic connection between Polycomb and Mxc has not been elucidated. Mutations in mxc also lead to loss of tissue maintenance, which is most evident in the male and female gonad. Here we find that loss of Mxc leads to changes in the ratios of key proteins, called histones, that are important for packaging DNA and, ultimately, for regulating gene expression. Our data suggest that changes in the ratio of histone proteins leads to persistent DNA damage, which contributes to loss of stem cells and failure to maintain tissues.

Scientific Abstract:
Polycomb group (PcG) proteins establish and maintain genetic programs that regulate cell-fate decisions. Drosophila multi sex combs (mxc) was categorized as a PcG gene based on a classical Polycomb phenotype and genetic interactions; however, a mechanistic connection between Polycomb and Mxc has not been elucidated. Hypomorphic alleles of mxc are characterized by male and female sterility and ectopic sex combs. Mxc is an important regulator of histone synthesis, and we find that increased levels of the core histone H3 in mxc mutants result in replicative stress and a persistent DNA damage response (DDR). Germline loss, ectopic sex combs and the DDR are suppressed by reducing H3 in mxc mutants. Conversely, mxc phenotypes are enhanced when the DDR is abrogated. Importantly, replicative stress induced by hydroxyurea treatment recapitulated mxc germline phenotypes. These data reveal how persistent replicative stress affects gene expression, tissue homeostasis, and maintenance of cellular identity in vivo.